Claims 6, 7, 11, and 17-21, also remain rejected for obviousness-type double patenting. Applicants address each outstanding rejection under its respective statutory section below.

Rejections Under 35 U.S.C. § 102

Claims 17-19 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Sytkowski *et al.* (*J. Biol. Chem.*, 262:1161-65 (1987); "Sytkowski"). Specifically, the Office continues to assert that Sytkowski discloses two neutralizing antibodies to EPO, anti-peptide 99-118 and anti-peptide 111-129, which allegedly bind to the receptor binding domain of EPO. In addition, the Office now provides new arguments for rejection of claims 17-19.

According to the Office, claim 17 is drawn to an antibody which binds to an epitope which binds to the EPO receptor ("EPOR"). As such, this claim does not specify that an isolated peptide, simulating an EPO epitope, must bind to the EPOR *in vitro* and elicit a biological effect. The Office further relies on Philo *et al.* (*Biochemistry*, 35:1681-91 (1996); "Philo") and Narhi *et al.* ((*J. Protein Chem.*, 16:213-25 (1997); "Narhi"), two new references, to hypothesize that the EPO protein may have two separate binding sites for the EPOR and that binding of the first site may be needed before binding of the second site can occur. Thus, the Office concludes that studies allegedly showing that sequential binding "do not rule out the possibility that these amino acid residues [99-118 and 111-129] when within the full length EPO protein directly bind to the EPO receptor." (Emphasis in original.) Applicants respectfully traverse the Office's rejection for the following reasons.

First, by making the current Office Action Final, the Office asserts that no rejections were based on new grounds. Applicants contend that the Office has improperly imposed finality. As the MPEP provides:

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> [A] second or any subsequent action on the merits in any application . . . will not be made final if it includes a rejection, on newly cited art, other than information submitted in an information disclosure statement filed under 37 CFR 1.97(c) . . . of any claim not amended . . . .

See MPEP § 706.07(a) (8th ed., Aug. 2001). Applicants note that no claims were amended in the previous response, dated December 21, 2001. Moreover, in maintaining its rejection of claims 17-19 under 35 U.S.C. § 102(b), the Office now uses two new references in addition to the previously cited reference, Sytkowski. These new references, Philo and Narhi, were not submitted in an Information Disclosure Statement during Applicants' prosecution of this patent application nor were they previously introduced into prosecution by the Office. As such, the Office did not formally cite Philo and Narhi, even though it should. *See In re Hoch*, 428 F.2d 1341, 1342 (C.C.P.A. 1970) (noting that where a reference is relied on to support a rejection, whether or not in a minor capacity, there is no excuse for not positively including the reference in the statement of rejection). Thus, by making the current Office Action final, the Office has acted inconsistently with its own procedures as set forth in the MPEP at § 706.07(a). Applicants therefore respectfully request that the Office withdraw finality of the current Office Action.

Second, as Applicants have consistently noted, Sytkowski clearly showed that peptides 99-118 and 111-129 do not directly bind the EPOR. Specifically, Sytkowski reported that the six peptides, used to generate their antibodies, failed to demonstrate any EPO biological activity and that these peptides failed to inhibit the biological activity of whole EPO. These six peptides included 99-118 and 111-129. More importantly, these authors directly state that "none of these peptides react[s] directly with the erythropoietin receptor" (p.1162, right column, first full

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paragraph). This is why Sytkowski considers alternative mechanisms by which antibodies to these peptides may be working. *See* page 1165 last paragraph.

Third, regarding the Office's interpretation of claim 17, this claim need not recite that an isolated peptide, simulating an EPO epitope, must bind to the EPOR *in vitro* and elicit a biological effect. Claim 17 is directed to an "anti-erythropoietin (EPO) antibody directed against epitopes that bind to the EPO receptor." An epitope is the specific portion of an antigen (i.e., a protein) to which an antibody binds. Thus, an epitope is a subset of the total peptide sequence of a complete antigen. As such, epitopes are short peptides that are part of the entire protein antigen sequence. The Office asserts that isolated peptides "simulate" an epitope in the full-length EPO protein. In contrast to this statement, Applicants assert that isolated peptides do not simulate an epitope, they *are* epitopes. Specifically, in Sytkowski, antibodies were generated by inoculating a host with the target peptides, 99-118 and 111-129. The resulting antibodies specific to those peptides bind them, making them epitopes. Likewise, Sytkowski shows that these antibodies bind the full-length EPO protein. Thus, these peptides are functional epitopes in the native protein. We note that, like Sytkowski, the specification also generated anti-EPO antibodies by inoculating a host with target peptides and shows that these antibodies bind full-length EPO.

Moreover, a skilled artisan commonly uses a biological test to detect a protein binding to its receptor when the biological functions of its receptor are known. We note that in addition to Sytkowski's biological function test, the specification also provides such a test at page 11, first full paragraph. Thus, a skilled artisan would commonly use an isolated peptide, functioning as an epitope, in conjunction with a biological test to identify an "anti-erythropoietin (EPO)

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antibody directed against epitopes that bind to the EPO receptor." These specific elements, however, need not be introduced into claim 17.

Finally, the Office's conclusion that the Philo and Narhi references "do not rule out the possibility" that Sytkowski's peptides, when in the context of EPO, may bind the EPOR is at most conjecture. The Office believes that Philo and Narhi teach that EPO has two binding sites for the EPOR and that when EPO binds the first site, a conformational change in either EPO or the EPOR occurs. Philo and Narhi present no data suggesting that this conformational change is necessary to allow a second EPOR to bind an EPO protein. In fact, Narhi concludes that the conformational change that supposedly occurs is very subtle and is not even sure if that change occurs in EPO or the EPOR. *See* page 224, first full paragraph. Thus, there is no evidence that this change is relevant to binding a second receptor. Moreover, Philo submits that their model of a second, low-affinity binding site in the EPO protein is inconsistent with the known models of EPOR dimerization. *See* page 1689, second full paragraph, lines 6-11; fifth paragraph, lines 1-3; and the last paragraph.

In sum, this rejection is improper on substantive grounds. The Office's characterization of Sytkowski's teaching remains inaccurate, as Sytkowski acknowledges his peptides do not directly bind to the EPOR. Applicants therefore request that the Office withdraw its rejection of claims 17-19 under 35 U.S.C. § 102(b).

The Office maintains its rejection of claims 5, 6, 11, 12, 17, 20, and 23 under 35 U.S.C. § 102(b) as allegedly anticipated by Lin (U.S. Patent 4,703, 008; "Lin"). The Office asserts that Applicants' quote from Lin, that "[p]reliminary *in vivo* activity studies on the three peptides revealed no significant activity either alone or in combination," is not evidence that the peptide 144-166 does not bind directly to the EPOR. The Office submits that Lin does not disclose that

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their antibodies have neutralizing activity, but contends that these antibodies would inherently be neutralizing. Regarding claim 17, the Office notes that this claim does not specify that the isolated peptide must bind the EPOR *in vivo* and elicit a biological effect. According to the Office, there are alternate reasons why a peptide may not bind the EPOR *in vivo*, including premature degradation of the peptide and an absence of conformational change that may be required for binding. Applicants traverse the Office's rejections on the following grounds.

First, as discussed above, claim 17 need not recite *in vivo* binding to the EPOR and the ability to elicit a biological function. Claim 17 does recite "epitopes that bind the EPO receptor." Such epitopes may demonstrate biological properties *in vivo*. As Applicants have previously indicated, Lin expressly indicates that the 144-166 peptide does not have *in vivo* activity. The Office tries to account for this inconsistency by proposing alternate explanations for why the 14-166 peptide lacks *in vivo* activity. Specifically, the Office proposes that the peptide may be quickly degraded *in vivo*, which is at best conjecture based on general knowledge in the art. The Office may not use such information. *See In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002) (holding that conclusory statements based on general knowledge or common sense cannot be used to overcome deficiencies of a reference). Thus, the Office's attempt to fill in this gap in reasoning in improper. The Office's also proposes that a conformational change may be needed in order for the 144-166 peptide to bind the EPOR, citing Philo and Nahri. For the reasons set forth above regarding Sytkowski, this hypothesis is without merit.

Second, regarding the contention that Lin's anti-peptide 144-166 antibodies are inherently neutralizing, Applicants respectfully contend that the Office has not used the correct standard for asserting inherency. The United States Court of Appeals for the Federal Circuit has addressed the issue of inherency. The court held that "in order for a claim to be inherent in the

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prior art it is not sufficient that a person following the disclosure sometimes obtain the result set forth in the claim, it must invariably happen." *Glaxo, Inc. v. Novopharm Ltd.*, 830 F.Supp. 871, 874, 29 USPQ2d 1126, 1128 (E.D.N.C. 1993), *aff'd,* 52 F.3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995) (emphasis added). In other words, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. §2112 (8th ed. 2001) (emphasis in the original) (*citing In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)). Instead, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described, and that it would be so recognized by persons of ordinary skill.'" *Id.* (emphasis added) *(citing In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). The Office has not met these high standards.

As Applicants noted in their previous response, peptide 144-166 represents a 50% increase in the number of amino acids over peptide 152-166. In contrast, the term "consisting essentially of" may include the claimed P2/1 peptide with a small number of amino acids added to it such that the new peptide generates the antibodies of the invention. For example, adding 8 amino acids to a peptide that is only 15 amino acids long will likely have more impact on the behavior of that peptide than those 8 amino acids will have on a peptide that is 100 amino acids long. The fact that Lin's 144-166 peptide has no *in vivo* activity supports the notion that this peptide does not present the 152-166 epitope properly. As such, just because the 152-166 sequence is contained inside the 144-166 sequence does not necessarily and invariably mean that the 144-166 peptide will generate antibodies that bind the 152-166 peptide or neutralize EPO activity. Thus, the Office has not met the high standards for rejecting a claim based upon

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inherency. As such, coupled with the Office's admission that Lin does not disclose neutralizing activity, this reference cannot anticipate independent claims 5 and 6.

Finally, regarding the Office's contention that it is "reasonable to conclude" that Lin's antibodies would react with the 152-166 peptide, this argument is again based on general knowledge in the art. As set forth above, the Office cannot use this type of rationale in rejecting the claim. Moreover, a standard of reasonableness falls far short of the strict requirements for inherency, should the Office argue that Lin's antibodies would inherently bind the 152-166 peptide. Applicants thus request that the Office withdraw its rejection of claims 5, 6, 11, 12, 17, 20, and 23 under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 103

Claim 10 remains rejected under 35 U.S.C. § 103(a) as allegedly upatentable over Sytkowski in view of Yanagawa *et al.* (*Blood*, 64:357-64 (1984); "Yanagawa"). According to the Office, Yanagawa teaches the production of three hybridomas secreting antibodies which bind to EPO. Yanagawa also allegedly teaches that one of these three monoclonal antibodies will be useful in purifying EPO. Applicants note that the Office has not responded to their prior argument regarding Sytkowski in light of this rejection. Applicants respectfully traverse.

The Office has changed its interpretation of Yanagawa. In the previous Office Action, the Office alleged that Yanagawa taught a method of purifying EPO based on monoclonal antibodies. Currently, the Office asserts that Yanagawa teaches the production of three hybridomas that secrete antibodies able to bind EPO and that one of these monoclonal antibodies "will be" useful for purifying EPO. Office Action, page 3, lines 9 and 10.

Claim 10 is not directed to antibodies that bind EPO. Rather, this claim recites a "method of using the antibody as claimed in claim 6 for purifying EPO . . . ." (Emphasis added.) As set

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forth in Applicants' previous argument, Yanagawa used chromatography columns to remove contaminants from their EPO source, followed by further purification of EPO by SDS-PAGE. In sum, Yanagawa teaches a method of purifying EPO, without the use of anti-EPO antibodies, in order to *produce* anti-EPO antibodies. In the end, Yanagawa did produce monoclonal antibodies that bind EPO. But the mere suggestion that one of these monoclonal antibodies will be useful in isolating EPO does not teach the method set forth in claim 10. The Office's use of future tense in its description of Yanagawa suggests that the Office realizes this reference does not teach such a method and that such a method has yet to be developed. Thus, Yanagawa either alone or in combination with Sytkowski cannot make claim 10 obvious. Applicants request that the Office withdraw its rejection in light of Applicants arguments.

Obvious-Type Double Patenting

Claims 6, 7, 11, and 17-21 remain rejected for obviousness-type double patenting over claims 1 and 2 of U.S. Patent No. 5,712,370. Applicants request that this rejection be held in abeyance until all allowable subject matter has been indicated.

Conclusion

Applicants respectfully request that this Response under 37 C.F.R. § 1.116 be entered by the Office, placing claims 5-7, 9-12, and 14-23 in condition for allowance. Applicants respectfully point out that the final action by the Office presented some new arguments and new references as to the application of the art against Applicant's invention. It is respectfully submitted that the entering of the Response would allow the Applicants to reply to the final rejections and place the application in condition for allowance.

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Furthermore, Applicants submit that the entry of the Response would place the application in better form for appeal, should the Office dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Response, the Office's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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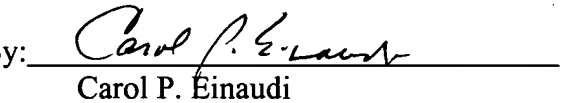
Dated: August 12, 2002

By: 
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